FROM THE RADIUMHEMMET, STOCKHOLMHEAD: PROFESSOR ELIS G. H. BERVEN

PREDISPOSING FACTORS FOR SQUAMOUS CELL CARCINOMA IN THE MOUTH, THROAT AND ESOPHAGUS. A STATISTICAL STUDY OF THE MATERIAL OF THE RADIUMHEMMET, STOCKHOLM[1]

by

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1. Introduction

Since the mucous membrane of the mouth, throat and esophagus are exposed much more often to chronic external irritation than most of the other organs, it is quite natural that cancer of the mucous membrane in these regions (squamous cell carcinoma) had been interpreted in the past as the effect of such an irritation. Numerous clinical experiences have supported the validity of the Virchow irritation theory with respect to these carcinomas. Ewing divides all carcinomas into two main groups: 1) those originating from embryonic organisms that have split off (Cohn - Heim - Ribbert tumor theory) and 2) those originating from chronic irritation of normal, adult cells. Ewing usually places the squamous cell carcinoma into the latter group. Almost all researchers regard in particular the carcinoma of the oral cavity as a result of chronic irritation (owing to tobacco, alcohol, poor teeth). However, these views vary when it is a question of evaluating the significance of this interpretation.

On the whole, the research community agrees that an irritation is the primary cause for socalled precancerous changes (e.g. leukoplakia and papilloma), which later develop into carcinomas.

A disposition for squamous cell carcinoma in the mucous membranes, which is our concern here, can also be induced by a number of other local pathological tissue changes, e.g. scar formations and atrophies and chronic inflammations, especially tuberculosis and syphilis and their resulting conditions. Billroth believed that

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carcinomas always appear in pathologically modified tissue. Precisely with respect to these carcinomas many researchers are inclined today to agree with him.

Despite the overwhelming theoretical interest in these questions and despite their practical significance -- in light of the possibility of prophylaxis for cancer -- clinical researchers have paid relatively little attention to these questions. Only a relatively small number of related problems may be regarded as having been definitively explained. For example, there is no consensus about the relatively simple question of how significant pipe smoking is with respect to lip cancer, even though it has been discussed since the 1790's when Soemmering first introduced it.

The clinical material of the Radiumhemmet is especially appropriate for statistical studies on the predisposing factors under discussion here. The clinic is a central institution for a significant portion of Sweden; and its material offers in most cases a good picture of the relative frequency in the whole population.

Recently we have also been able to obtain more insight into the significance of a factor that was not very well known earlier, yet affects the carcinoma under discussion here. I am referring to a specific type of hypochromic anemia in women (simple achylanemia and the Plummer - Vinson syndrome). These experiences, (published by Ahlbom), have been largely the reason for our becoming more interested in predisposing factors than was the case earlier. The purpose of the present paper is a statistical study of these factors, especially in light of recent findings on the aforementioned anemic conditions in women.

Since the latter factor in our material was not studied in detail before 1931, only cases treated since the beginning of 1931 have been included. If the necessary data was absent from the medical history, we tried to fill in the gaps through followup examinations. A significant number of patients have died in the interim, before such followup examinations could be carried so that some gaps were unavoidable.

2. Frequency and Sex Distribution in Various Countries

It seems to follow from a number of morbidity statistics, published in Europe and the U.S.A., that approx. 10 to 15% of all carcinoma develop in the lips, mouth
cavity, pharynx, larynx, and esophagus. The relative frequency of these individual locations varies widely in the data, even when the cases are from one and the same country. This fluctuation suggestions that the

material is selected to some extent and that the categorization criteria also differ. The large morbidity statistics are not very important for the evaluation of the distribution because, for example, the morbidity rate for hypopharyngeal carcinoma is much higher than for lip cancer. At the same time the lip seems to be the most frequent site for cancer in every country. The second most frequent sites for cancer are the tongue, esophagus, and larynx. In Germany and in Switzerland cancer of the hypopharynx, larynx and esophagus occurs relatively more frequently than in Sweden (Strauss and Schinz and Senti). In some American morbidity statistics the number of carcinomas of the tongue and other parts of the oral cavity is relatively high. Pack and Le Fevre (Memorial Hospital, New York) have documented, for example, the following numbers: lip carcinoma: 589 cases, tongue carcinoma: 788, other types of carcinoma of the mouth: 636, carcinoma of the esophagus: 421. Nyström compiled the following morbidity statistics in Sweden for 1911 and 1912: lip carcinoma: 275 cases, carcinoma of the tongue: 59, other carcinoma of the mouth: 91, esophagus carcinoma: 237 (cardia carcinoma is included in the latter figure). The material of the Radiumhemmet from 1931 to July 1936 includes lip cancer: 338 cases, cancer of the tongue and the floor of the mouth: 174, other oral carcinomas: 164, mesopharyngeal and hypopharyngeal carcinoma: 155, laryngeal carcinoma: 55, esophageal carcinoma: 40. However, the figure for cancer of the esophagus is certainly lower than the actual frequency, since this type of tumor often goes untreated.

When the issue is to study the significance of the predisposing factors and above all the chronic irritation associated with cancer of the mouth, throat and esophagus, statistical conclusions about the sex distribution in tumor cases are of greater interest than the total frequency figures. Heavy consumption of tobacco and alcohol was very unusual in women, at least up to recently; and one is also of the opinion that the frequency of syphilis is generally significantly lower in women than in men. In most countries only a relatively small minority of these cancer cases involves women; and this fact constituted one of the strongest pieces of evidence for the validity of the irritation theory. The figures for the different cancer sites and the different countries exhibit interesting variations with respect to their frequency in men and women. These variations are easy to study, since the literature abounds with data about sex distribution. Moreover, the data are also significantly more reliable than general frequency figures, since the sex distribution does not generally have
significant sources of error. Of the numerous statistical data that are published, I have selected here only a few typical examples from research based on voluminous material. For the sake of comparison the following list also includes our series of the Radiumhemmet.

I. Cancer of the lip
Switzerland (Schinz and Senti)23% Women
U.S.A. (Fricke)10% "
Sweden (Radiumhemmet)7% "
Argentinia (Roffo)7% "
U.S.A. (Pack and Le Fevre)6% "
Netherlands (Wassink)4% "
U.S.A. (Broders)2% "

II. Cancer of the tongue
Sweden (Radiumhemmet)40% "
Netherlands (Wassink)15% "
U.S.A. (Pack and Le Fevre) 13% "
U.S.A. (Taylor) 11% "
France (Sebileau)5% "
Switzerland (Schinz and Senti)3% "

III. Cancer of the mouth (except for lip cancer)
Sweden (Radiumhemmet)43% "
Germany (Strauss) 30% "
Germany (Küttner) 19% "
U.S.A. (Taylor) 10% "

IV. Mesopharyngeal and hypopharyngeal cancer
Sweden (Radiumhemmet)57% "
U.S.A. (New and Childrey) 12% "
Switzerland (Schinz and Senti) 9% "

V. Cancer of the larynx
Sweden (Radiumhemmet)15% "
Switzerland (Schinz and Senti) 5% "
Netherlands (Wassink)4% "

VI.Cancer of the esophagus
Sweden (Radiumhemmet)40% "
Germany (Strauss) 22% "
U.S.A. (Pack and Le Fevre) 20% "
Switzerland (Schinz and Senti) 9% "

The above data and voluminous other data in such papers reporting on smaller volumes of material can be summarized and grouped as follows:

1) One group of countries, represented by France, Italy and Switzerland, exhibits a very low ratio of women in this cancer group (5 to 10%). In Switzerland, however, lip cancer constitutes an exception because there was an unusually high number of female cases (23%). 2) In another larger group of countries (England, Germany, Austria, the Netherlands, Denmark) 20 to 30% of the women participated in this cancer group. 3) A small third group, represented by Sweden and perhaps also by Norway and Finnland, exhibits on the whole virtually just as many women as men. However, Sweden exhibits almost the same sex distribution of cancer of the lip and the larynx as other countries. In contrast, the Swedish material reveals the significant feature that the women constitute the *majority* of the hypopharyngeal carcinoma cases (approx. 60%). If the hypopharyngeal carcinomas are divided into two groups -- the high and deep seated --, this unusual proportion of high seated carcinomas disappears. They are represented by only 20% of the women in the material of the Radiumhemmet. Instead, the female majority -- almost 90% -- exhibits the deep seated carcinoma (according to the English nomenclature "postcricoid carcinoma"). This tendency of the postcricoid carcinoma to affect in particular women is not unusual for Sweden. According to a large compilation by Turner, 85% of 98 English patients with postcricoid carcinoma were women. Smaller statistics from Germany, Denmark and the Netherlands also reveal a female majority, even if not as striking as in the English and Swedish material. On the other hand, in France (Coutard et al.) hypopharyngeal carcinoma in female patients and thus also the postcricoid type are rare. The striking ratio between Swedish men and women in relation to the frequency in the whole group of hypopharyngeal carcinoma is based on the fact that Sweden has a high occurrence of postcricoid carcinomas - a type of tumor that is rather characteristic for women.

We shall find in the following presentation of the different predisposing factors that it is possible to clear up to some degree what appears to be a rather random sex distribution of these squamous cell carcinomas, described here.

3. Lip Cancer

As stated above, as early as the end of the 18th century it was noticed that lip cancer frequently afflicts pipe smokers. On the other hand, many authors have expressed recently grave doubts about the etiological significance of pipe smoking.
It has been pointed out that pipe smoking is so wide spread that it is not possible to obtain statistical proof of its harmful effect. It seems that Pack and Le Fevre, for example, who studied a large volume of material, do

not want to attach any great importance to pipe smoking as a predisposing factor. Like some other authors, they are of the opinion that solar radiation is the most important factor, just as in the case of squamous cell carcinoma of the skin. This author believes that men develop lip cancer much more frequently than women because men are more likely to exhibit a certain prognathism than women. Thus the lower lip of men would get more sunlight.

The age of male patients of the Radiumhemmet ranged in general from 60 to 80 years old. Usually they had consumed tobacco continuously for a prolonged period, as a rule 30 to 40 years. As evident from the percentages of the following table (Table 1), 57% were pipe smokers. It follows that pipe smoking is not a necessary condition for a man to develop lip cancer. In contrast, the percentage of pipe smokers is conspicuously high among the patients with lip cancer as compared to the male patients with cancer in other regions.

Table 1

Male Patients at the Radiumhemmet from 1931 to 1936[1]

	Lip Cancer 812 cases tobacco consumption in 86%	Cancer of the mouth cavity, larynx, pharynx and esophagus 233 cases tobacco consumption in 98%
Pipe smoking	57%	25%
Cigar and cigarette smoking	6%	40%
Snuff and chewing tobacco in the mouth	37%	35%

Our material agreed rather well with the Broders material, comprising 537 cases. Eighty percent of the men of his series consumed tobacco, of which 78% were pipe smokers. Of the 500 men without cancer, 80% were also tobacco consumers, but only 35% of them were pipe smokers.

Nyström notes in his research on cancer diseases in Sweden (statistics from 1911 and 1912) that lip cancer is the only form of cancer that occurs much more

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[1]In this table, as also in the following tables, there are no cases, lacking data on tobacco consumption, etc.

frequently in rural areas than in urban areas. He correlated this finding with the fact that the frequency of pipe smoking and tobacco chewing is significantly higher in the country than in the cities. In this respect he may have overlooked that there is also another possibility, namely that work

outside the house may be a predisposing factor for lip cancer, e.g. due to the impact of the sun.

In the material of the Radiumhemmet, starting from 1931, almost 90% of the men with lip cancer were farmers, agricultural workers, forestry workers, fishermen, etc. In the group of male patients with cancer of the oral cavity, only about 30% were individuals who worked outdoors. In contrast, only 10% of the male patients with cancer of the larynx, hypopharynx and esophagus had carried out their job in the open air (almost 90% were city dwellers).

These differences in the distribution are, to be sure, quite significant, and one raises the question whether outdoor work is the most important factor for lip cancer. Then the relatively large number of pipe smokers would simply be based on the fact that these farmers etc. smoke pipes more frequently than the city dwellers. To answer this question, we must investigate what the situation is with the female patients.

Since 1931 we have treated 23 women suffering from lip cancer. Almost all of them were country dwellers. *Of these more than half (12) were avid pipe smokers.* In this case the frequency of pipe smoking was just as high as for men. In Sweden pipe smoking by women is a dying practice of the past and occurs actually only in certain remote wooded areas. Hence, it is fairly safe to assume that not even one percent, perhaps one Swedish female per million in the carcinoma age, is a pipe smoker.

Even though our series of female lip cancer cases includes only 23 cases, it may, nevertheless, be regarded as proof that pipe smoking is actually an important predisposing factor. Nyström found that 20% of the lip cancer patients in Sweden in 1911 and 1912 were women. Now the figure has declined to 7%. It is possible that this steep drop in the relative number of women is due to the fact that pipe smoking in women, as stated above, is dying out. According to Schinz and Senti, as already pointed out, Switzerland has a conspicuously high number of women with lip cancer (23%). Perhaps it correlates with the practice that in some regions of the Alps, as Haberer has reported, women tend to smoke a pipe to the same degree as the men.
If the consumption of tobacco and above all pipe smoking is a significant factor for the development of lip cancer, then it would be just as certain that there must be also other predisposing factors. Since in Sweden lip cancer together with squamous cell carcinoma of the skin is the sole type of cancer that is characteristic of the rural regions, there is the tendency to see the predisposing factor in the chronic irritation caused by "weather and wind" and above all solar radiation. Finally one must consider still

another condition, namely that these old country dwellers suffer almost continuously from pyorrhea alveolaris and very bad teeth. Syphilis does not seem to play an important role in our lip cancer material.

The correlation between prognathism in men and the effect of sunlight, which Pack and Le Fevre just recently stressed, can, of course, have some significance. However, a more obvious explanation for the ratio between male and female lip cancer cases seems to be that the women in the country spend much less time outside the house than the men.

In a couple of the female patients of the Radiumhemmet lip carcinoma occurred together with one other form of mouth cancer in the presence of the Plummer - Vinson syndrome. This syndrome seems to play a rather unimportant role as a predisposing factor in lip cancer.

In some of the male patients it seems as if the carcinoma developed in scars following trauma, burns or frostbite.

4. Cancer of the Oral Cavity in Men

Owing to the special importance attributed to syphilis as the predisposing factor for cancer of the tongue, studies of this type tend to divide carcinomas of the oral cavity into two groups. The alveolar process of the upper jaw is often the seat of squamous cell carcinoma. Since it is difficult to distinguish which cases of this group are truely carcinomas of the oral cavity and which proceeded from the maxillary sinus, the whole group has been excluded from this compilation.

a) buccal carcinoma, gingival carcinoma and carcinoma in the alveolar process of the mandibule ("carcinoma of the external oral cavity").

In Sweden these carcinomas tend to afflict the rural population, even though not in the same high magnitude as lip carcinoma. Of the men of this group 60 to 70% were farmers and other persons dwelling in the country. Almost all of the
patients reported prolonged and high consumption of tobacco. The following table (Table 2) shows the different types of consumption.

Table 2

Male Patients at the Radiumhemmet from 1931 to 1936

	Buccal, gingival and mandibular carcinoma 68 cases tobacco consumption in 98%	Lip carcinoma 312 cases tobacco consumption in 86%
Pipe smoking	23%	57%
Cigar and cigarette smoking	7%	6%
Snuff and chewing tobacco in the mouth	70%	37%

As evident from the table, in this group chewing tobacco is a relatively bigger factor than pipe smoking for lip carcinoma. If the individual cases are closely analyzed, the predisposing effect of tobacco chewing becomes even more impressive. In most cases the tobacco or snuff tobacco was in the same place in the mouth every day, at times even during the night, for a period of 30 to 40 years. Usually these carcinomas developed *at the exact location where the tobacco had lain* (in at least 70% of the cases). At times the patients reported that they had moved the tobacco alternatingly from the right to the left side. In some of these cases we observed well defined leukoplakia on the one side, precisely where the tobacco had lain, and a carcinoma, surrounded by leukoplakia, at the symmetrical location of the other side. In some cases the patients reported even spontaneously that they often tended to put the tobacco where later the carcinoma developed rather than on the other side. If the carcinoma had not spread too far, residual "tobacco leukoplakia" could be found on the periphery of the tumor. In the case of buccal and gingival carcinomas the association with leukoplakia was even more obvious and could be demonstrated more often than in the case of the other squamous cell carcinomas, under discussion here. Frequently they are also exophytic and papillomatous.

The majority of the patients concerned had very bad teeth and pyorrhea alveolaris.

One single patient of this group had not consumed any tobacco. This patient had a positive Wassermann reaction. Otherwise there were only 3 patients, whose medical history and serology suggested syphilis.
Alcohol abuse was, as far as we could determine, not present to any significant degree in patients of this group.

Several authors, for example Ewing, Taylor and Martin and Pflueger, have expressed the opinion that buccal carcinoma correlates well with chronic irritation (primarily due to tobacco and poor teeth).

Davis reported that cheek carcinoma in the Philippines develops more often in women than in men. He traces this to buyo chewing, to which precisely the women on this islands are addicted (buyo: a mixture of buyo leaves, betel mixed with chalk and tobacco).

b) Carcinoma of the tongue, floor of the mouth, and gums ("carcinomas of the inner oral cavity").

Approximately 70% of the men of this patient group were city dwellers. Most of the patients had poor teeth and pyorrhea alveolaris, even if this finding was not as routine as in the two previous groups. Of course, the oral hygiene of the city dwellers is on a somewhat higher level than that of the farmers.

The percentage of tobacco consuming patients was not much under 100 (see Table 3). Since the majority of the patients were city dwellers, it is not surprising that cigar and cigarette smoking formed a much higher percentage of tobacco consumption than in the two previous groups.

Table 3

Male Patients at the Radiumhemmet from 1931 to 1936

	"Carcinoma of the inner oral cavity" 78 cases tobacco consumption in 96%	"Carcinoma of the outer oral cavity" 68 cases tobacco consumption in 98%	Lip carcinoma 312 cases tobacco consumption in 86%
Pipe smoking	35%	23	57%
Cigar and cigarette smoking	39%	7%	6%
Snuff and chewing tobacco in the mouth	28%	70%	37%

Apparently there is a low probability that cigar and cigarette smoking constitute a higher disposition for carcinoma of the tongue and gums than the other forms of tobacco consumption. It is more likely that cigar and cigarette smoking is only a "concomitant phenomenon", when the more specific predisposing factors in city dwellers, namely alcohol and syphilis, begin to have a greater impact.

It is difficult to make a somewhat objective statement about the frequency of alcohol abuse in patients. In the interim we have gotten the distinct impression
that the men of this group (of which the majority had tongue cancer) usually consumed a rather high volume of alcohol. The medical history

revealed positive alcohol abuse or alcoholism in 14% of the cases. This figure is certainly much too low.

Almost all of the authors emphasize in this respect that tongue cancer frequently develops owing to syphilitic changes. We found 30% as the frequency of syphilis in the tongue carcinoma cases, a high number for Swedish conditions. In one of the 13 men with gum carcinoma the medical history pointed to syphilis. German and American authors have reported 20 to 40% as the frequency of syphilis based tongue carcinoma (Ehrlich, Bloodgood, Lund, Taylor et al.). In France and Italy, where tongue carcinoma occurs virtually exclusively in men, syphilis seems to occur much more often in these cases. Sebileau makes the sweeping statement that three factors are as good as necessary for the development of tongue cancer -- namely male sex, syphilis and heavy smoking.

5. Carcinoma of the Oral Cavity in Women

In the case of lip cancer we found that more than 50% of the women had smoked a pipe. Of 132 women, who were treated for carcinoma of the oral cavity, only 15% had consumed tobacco. Even these cases usually involved pipe smoking. Even if this frequency of pipe smoking is so high that it must be regarded as proof for a certain degree of predisposing effect, it is still clear that it does not "explain" the majority of these cases. Syphilis is a less relevant factor than in the corresponding group of men, since we found reference points for this disease in only 3 to 4 cases. Moreover, alcohol abuse could be demonstrated in only one single case.

In light of these circumstances and the fact that in Sweden there are just as many cases of oral carcinoma in women as in men, it is tempting to question the significance of the irritation theory, even with respect to carcinoma of men. We will argue in the following that this is not necessary because there is a predisposing factor that is as good as specific for women and that is so important that it can actually explain the large number of cases in this group.

The pipe smoking female patients were 70 to 80 year old farm women. The other women were younger, 40 to 70 years old. (Average age was approximately 55 years). In somewhat more than half of these cases the women were from the country.
Almost all of these women were toothless, and most of them had worn dentures in the upper and lower jaw for many years.

Taylor, who had studied a large volume of American material, found, as we did, that the tobacco, alcohol and syphilis factors, which are virtually

constant in men, were grossly inadequate for explaining the female cases. He could also verify that toothlessness in women was quite frequent. Thus, he drew the conclusion that irritation caused by dentures is an important predisposing factor in these cases.

Our interpretation of these conditions is totally different. Toothlessness is not an indirect cause of carcinoma, but rather one of the symptoms of a disease whose sequela is oral carcinoma. The underlying disease is a chronic hypochromic anemia, which occurs almost exclusively in women. It often begins between the ages of 18 and 20, but can also develop later, but not after the age of 50. The literature tends to distinguish between two types of this disease -- simple achylanemia and the Plummer - Vinson syndrome. The most important symptoms of simple achylanemia are (besides hypochromic anemia and achylia): early (at the age of 20 to 30) toothlessness, atrophy of the lips, the mucous membrane of the mouth and above all the mucous membrane of the tongue (in the advanced stages smooth tongue), fissures in the labial angles and in certain cases nail change (brittle, flat nails or concave nails - koilonychia) and enlargement of the spleen. The Plummer - Vinson syndrome exhibits very similar symptoms (achylia may, however, be lacking at times) and dysphagia. The dysphagia is manifested in constant difficulty swallowing larger bites of solid food (bread, meat, fruit, potatoes). In severe cases the patients are afraid of solid foood, since it tends "to stick in the throat" and they live exclusively on liquid food. The patients call this symptom "constricted throat" and it is not difficult to distinguish this dysphagia from "globus hystericus". The anatomical basis of dysphagia is atrophy of the mucous membrane of the hypopharynx and the entrance of the esophagus. It is probably the same type of change that results in a smooth tongue. The entrance into the esophagus is narrow and inflexible, a condition that can be easily observed with x-ray fluoroscopy, when relatively solid contrast lumps ("bolus") are administered.

The author is convinced that simple achylanemia and the Plummer - Vinson syndrome are one and the same disease. If one carefully researches the medical history, one will also often find in those cases, called simple achylanemia,
symptoms of mild or perhaps only indicated dysphagia.

Owing to the aforementioned atrophic mucous membrane changes, this chronic anemic condition becomes a precancerous disease, perhaps in the same manner as lupus develops through atrophy to squamous cell carcinoma.

Mc Gibbon has published a case of Plummer - Vinson syndrome with carcinoma degeneration in the mouth; and Wassink has reported some cases of cancer of the mouth in women, where the medical history clearly shows that the Plummer - Vinson syndrome was present.

In 1931 we noticed the precancerous properties of these conditions, and since then we have confirmed a rather large number of such cases among female patients with cancer of the oral cavity (Table 4).

Table 4

Female Patients with Cancer of the Oral Cavity at the Radiumhemmet, 1931 - 1936

All Cases	Of Which Pipe Smokers	Studied for Anemic Conditions	Of Which Plummer - Vinson Syndrome	Simple Achylanemia
132	20	88	37	9
	(15%)		total **46 - 53 %** of the studied patients	

Among the relatively small number of closely examined women, who had consumed tobacco and showed no signs of the Plummer - Vinson syndrome (approx. 30), there were two with positive Wassermann reaction in the blood and some others, who exhibited clear signs of mechanical irritation due to decayed teeth or defective dentures where the carcinoma had developed. If one also considers that the diagnosis -- simple achylanemia or syphilis -- could have been very easily overlooked in some of these cases, one must say that the female material of oral carcinoma cases exhibited the male predisposing factors of the different type to just about the same high degree.

If the Plummer - Vinson cases and the female pipe smokers are excluded from our female group of patients with cancer of the oral cavity, the remainder is so small that the ratio between male and female cases of mouth cancer is
approximately the same as in the majority of the other European countries (approx. 12%).

The author is convinced that in Sweden the anemic conditions under discussion are more frequent or severer than in other countries and this is the reason why in Sweden there is such a relatively high number of women with carcinoma of the mouth. However, one will probably also find in other countries that a significant number of female cases with carcinoma of the mouth can be correlated with the aforementioned predisposing factor. For the Netherlands, Wassink has also demonstrated this; and Taylor's data about the almost constant toothlessness of his

female patients may indicate that the same factor is also effective in American women.

6. Carcinoma in the Mesopharynx, Hypopharynx, Larynx, and Esophagus in Men

In this respect these patients formed a natural group, since approx. 90% of the total number were city dwellers. Whereas the lip cancer patients were largely country dwellers, only relatively few men of this group were of this profession, whereas it was striking that they often were salemen, travelling businessmen, restaurant personnel and military personnel. In a rather large number of cases, 36% (49 of 137) obvious alcohol abuse or alcoholism could be confirmed. Since it is often quite difficult at times to get any information in this respect, it can be assumed that the number is really noticeably higher. In Swedish cities alcohol abuse is much more frequent than it is in the farming population. Therefore, it is clear that alcoholism in city dwellers may be regarded as one of the most important predisposing factors for these carcinomas.

Of the 87 patients that belonged to this group and questioned about tobacco consumption, there was one patient who had abstained. Usually the consumption was rather intensive. Many patients reported that they had smoked 20 cigarettes or more per day. The type of tobacco consumption follows from the data of the following table, which for comparison purposes also shows the already discussed groups.

The author finds it difficult to imagine that the large number of cigar and above all cigarette smokers has any other meaning than that we are dealing predominantly with city dwellers here. It is quite likely that alcohol consumption and heavy smoking (irrespective of which type of tobacco) are relevant factors in the development of these carcinomas.

Table 5

Male Patients at the Radiumhemmet 1931 - 1936 (All Groups)

	Lip cancer 912 cases tobacco consumption in 86%	"Carcinoma of the outer oral cavity" 68 cases tobacco consumption in 98%	"Carcinoma of the inner oral cavity" 78 cases tobacco consumption in 96%	Carcinomas in the pharynx, larynx and esophagus 87 cases tobacco consumption in 99%
Pipe smoking	57%	23%	35%	20%
Cigar and cigarette smoking	6%	7%	39%	64% [1]
Snuff and chewing tobacco in the mouth	37%	70%	26%	16%

Syphilis could be confirmed in 14 cases (10%). One patient developed cancer in a cicatricial stricture following injury suffered in childhood from etching. Two patients, both of whom were smokers, but did not drink a lot of alcohol, exhibited certain symptoms that were suggestive of simple achylanemia in one case and the Plummer - Vinson syndrome in the other case. The one patient had been treated for many years for achylia and "secondary anemia". The other had also suffered for many years from mild dysphagia. Both had lost their teeth early; both were pale and thin. Both had finally deep seated hypopharyngeal carcinomas, a localization that is quite unusual for men.

7. Carcinoma in the Mesopharynx, Hypopharynx, Larynx, and Esophagus in Women

If only the same factors that we could detect in men -- alcohol abuse, tobacco consumption, and to some degree syphilis -- had an impact in women, then the number of cases in this group should be rather small. However, this was not the case. The entire group comprised 137 men and 113 women (45% women). If one studies the sex distribution for the different localizations, one finds that the large number of women is explained especially by one localization, namely hypopharyngeal carcinoma, which follows from the figures in the following table.

Of the 50 hypopharyngeal carcinomas in men only a relatively few, approx. 10%, could be classified as deep seated. Of the 74 hypopharnygeal carcinomas in women, on the other hand, the large majority, approx. 90%, were deep seated. Completely

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[1] 15 smoked predominantly cigars, 41 cigarettes.

Table 6

Radiumhemmet 1931 - 1936

	Number of Cases	
	Men	Women
Tonsillar carcinoma	16	7
Other mesopharyngeal carcinomas	0	8
Hypopharyngeal carcinoma	50	74
Laryngeal carcinoma	47	8
Esophageal carcinoma	24	16

accurate figures cannot be given here, because it was not always easy, especially with large tumors, to note with accuracy the localization. Thus

we find that given a narrow definition the deep seated hypopharnygeal carcinoma ("the postcricoid carcinoma") explained the large number of women in this group. We also include those tumors that extend to the uppermost part of the esophagus.

We could not find that tobacco consumption in women with mesopharyngeal, hypopharyngeal and esophageal carcinoma was a factor. Only 4 female patients smoked a pipe. Alcohol consumption could not be confirmed in any of the cases; and syphilis seemed rare in these women. Of the 8 female patients with laryngeal carcinoma one had smoked cigars and one had smoked a pipe.

In contrast, the association with the Plummer - Vinson syndrome and simple achylanemia was even clearer in this group than for mouth cancer. It was particularly obvious with respect to deep seated hypopharyngeal carcinomas, which had apparently developed on the basis of these anemic conditions in almost 90%. This predisposing factor gives a totally adequate "explanation" for the disproportionately large number of women with this carcinoma localization. These carcinomas develop at the transition point between hypopharynx and esophagus, behind the cricoid cartilage. Precisely in this area the women, suffering from the Plummer - Vinson syndrome, localize their difficulties with swallowing. In this area the atrophy, shrinkage or the change in elasticity develops the most noticeably. It is probable that here, too, the mucous membrane is highly irritated by the difficult passage of food. Thus, it is not surprising that the squamous cells tend to degenerate precisely in this location.

Another cancer localization is also very typical as the resulting condition of the syndromes under discussion, namely carcinoma on the rear wall of the
mesopharynx. In isolated cases these tumors also develop in the side wall, for example behind the tonsillar region. This carcinoma is usually a wide spread papillomatous tumor crawling along the surface. At times the relatively thin tumor plate can be traced as far as into the nasopharynx. In men we have not seen any cases of this type. Of the 8 female women with this mesopharyngeal carcinoma unfortunately 3 were not examined in detail for the Plummer - Vinson syndrome and could not be examined later, since they had died. All of the other 5 had distinct signs of this disease.

Otherwise the frequency of the Plummer - Vinson syndrome and simple achylanemia follows from the data of the following table.

Table 7

Female Patients at the Radiumhemmet from 1931 - 1936

	Number of Cases	Not closely examined for anemic conditions	Examined patients	Plummer - Vinson syndrome	Simple achyl-anemia	Negative
Tonsillar carcinoma	7	2	5	3	0	2
Other mesopharyngeal carcinoma	3	3	5	5	0	0
Hypopharyngeal carcinoma	74	25	49	37	5	7
Laryngeal carcinoma	8	0	8	1 (?)	1 (?)	6
Esophageal carcinoma	16	10	6	3	0	3
Total	**113**	**40**	**73**	**49**	**6**	**18**
				55 = 75% of the examined patients		

The 18 "negative cases" form a rather small portion of this group. Among these 18 women there were also at least 3, who were rather heavy smokers. It may be that in some of the other cases a simple achylanemia or a syphilitic infection had remained undiagnosed in the medical history.

Wassink, who emphasized in two papers (1933 and 1935) that women with carcinoma in the entrance of the esophagus and in the bottom part of the hypopharnyx are often characterized by a specific type or a specific constitution (narrow mouth opening, toothlessness, smooth tongue, chronic dysphagia, etc), has recently identified in a presentation at the Second International Cancer Congress in Brussels (September 1936) this constitution as hypochromic anemia or
Plummer - Vinson syndrome. Wassink was so kind as to let me inspect some unpublished statistical data about these relationships from the Antoni van Leeuwenhoek-huis in Amsterdam. These statistics are presented in the following data:

hypopharyngeal carcinoma178 men, 21 women
carcinoma in the uppermost part of the esophagus32 men, 33 women

Of the 21 women in the first group, 6 were thoroughly examined for "hypochromic anemia". One of the 6 female patients exhibited signs of having had this disease. Of the 33 women in the second group, 26 had been thoroughly examined and 17 of them had "hypochromic anemia" or the Plummer - Vinson syndrome. The localization, which Wassink calls "carcinoma of the uppermost part of the esophagus", is assigned to the

bottommost part of the hypopharynx in the Radiumhemmet. Taking this into consideration, the material agrees quite well with the Swedish material, even though the number of women is relatively smaller than in our case.

8. Summary and Conclusions regarding Prophylactic Measures

A lifetime of outdoor work predisposes -- probably primarily due to the effect of the sun -- to lip cancer. Poor oral hygiene, tooth decay and pyorrhea alveolaris are certaintly important contributing causes for the development of lip cancer and cancer of the oral cavity both in men and also in women, even though this can hardly be determined statistically with the material of the Radiumhemmet. Heavy tobacco and alcohol consumption and syphilis are important predisposing factors for squamous cell carcinoma in the entire upper part of the digestive canal and the larynx, above all in men, up to a certain degree, however, also in women. Simple achylanemia and the Plummer - Vinson syndrome are very important factors for Swedish women as a predisposing factor, in particular with respect to mesopharyngeal and hypopharyngeal carcinomas, but also for carcinoma of the oral cavity.

The curves from Figures 1 to 3 give an overview of these relationships.

The conclusions drawn with respect to prophylactic measures for carcinoma are largely self-evident. Measures to improve oral hygiene and tooth care, war against syphilis, propaganda against alcohol and tobacco and above all against immoderate tobacco and alcohol consumption must be naturally the main points of the program to prevent these forms of cancer. This program does not contain anything new, but the significance of this program is not as widely

Figure 1: Male Patients at the Radiumhemmet from 1931 to 1936

Tobacco consumption

City dwellers

Alcohol abuse

Syphilis

Lip cancer	Cancer of the outer oral cavity	Cancer of the inner oral cavity	Cancer of the pharynx, larynx, and esophagus

Figure 2: Male Patients at the Radiumhemmet from 1931 to 1936

City dwellers

Cigar and cigarette smoking

Pipe smoking

Snuff and chewing tobacco in the mouth

Lip cancer	Cancer of the outer oral cavity	Cancer of the inner oral cavity	Cancer of the pharynx, larynx, and esophagus

Figure 3: Female Patients at the Radiumhemmet from 1931 to 1936

Plummer - Vinson syndrome and simple achylanemia

Pipe smoking

Lip cancer	Cancer of the oral cavity	Laryngeal cancer	Mesopharyngeal and hypopharyngeal cancer	Esophageal cancer

accepted as it should be.

We can also establish a prophylactic program for the numerous female cancer cases, which have to be associated with simple achylanemia and the Plummer - Vinson syndrome. We know with certainty that administering iron in large doses can ameliorate these anemias quickly and safely. In this manner the condition of the mucous membranes (at least in stages that are not too well advanced) would also improve. It is quite likely that early diagnosis, effective therapy and conscientious followup in these cases could prevent the development of many carcinomas. The actual etiology of these anemic conditions is still unknown and hence one cannot speak about causal therapy. If there were causal therapy, one could actually design a rational prophylactic cancer program in this area. A number of circumstances support the idea that deficient intake or weakened resorption of iron is an important etiological moment. Women have, of course, a greater need for iron than men. In this respect it is interesting to note the fact that the poor

population of Sweden lives on a diet that is usually low in iron and one sided. Several authors suspect that not only iron deficiency but also vitamin deficiency can be a relevant factor. The syndromes under discussion seem to be especially frequent in Sweden; and according to the carcinoma cases, they occur more frequently in the poorer classes than in the affluent classes. In the material of the Radiumhemmet the ratio between the number of men and women for the carcinoma groups under discussion is approximately 1 to 1 in the poorer patients, but approximately 5 to 1 in the private patients. Among the approximately 100 cases of the Plummer - Vinson syndrome and simple achylanemia with carcinoma, which we diagnosed since 1931, there were only 4 private cases, a significantly smaller ratio. To the aforementioned, perhaps somewhat utopic proposals for better hygiene with respect to tooth care, alcohol, tobacco, etc. we would also like to add one more point with respect to cancer in women, namely a better diet. What is missing in the diet of the poorer Swedish population is primarily iron-containing vegetables, fruit and meat.

As long as we do not know the most in depth cause of the carcinomas under discussion, we can only hope to reduce the frequency somewhat through prophylactic measures. At the same time the fact that in particular the carcinoma groups discussed here could be effectively treated by preventive measures, if they could be carried out effectively and practically, is quite promising.

(translator's note: see English language summary and literature)